IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re patent application of Glennon and Hellburg

Serial No. 10/526,076 Group Art Unit 1625 Conf. #: 8312

Filed: October 24, 2005 Examiner Covington

For "ß-HYDROXYPHENYLALKYLAMINES AND THEIR USE FOR TREATING GLAUCOMA"

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION UNDER 37 C.F.R. § 1.132
OF DR. RICHARD A. GLENNON

Sir:

1. I hold a PhD in Medicinal Chemistry (1973) from the School of Pharmacy at the State University of New York in Buffalo, New York.

2. As can be seen from my attached *Curriculum vitae*, I have held a number of positions in the field of medicinal chemistry throughout my career, and I am currently Chair of the Department of Medicinal Chemistry at Virginia Commonwealth University in Richmond, Virginia. I am considered an international expert in drug design. I have authored more than 350 peer-reviewed articles and more than 50 textbook chapters. I have edited several books related to medicinal chemistry, and I am inventor of 13 issued United States patents. I thus qualify as an "expert" in the field of medicinal chemistry and drug design, and I am able to provide evidence on matters pertaining to medicinal chemistry and on the level of one of ordinary skill in the art.

3. I am an inventor of and have reviewed the subject patent application, including the claims, and the Examiner's remarks as contained in the Office Action mailed on January 22, 2009.

4. Regarding the Examiner's opinion that substitutions in a molecule, such as replacement of a hydrogen atom with methyl group, is normally within the sphere of obviousness that surrounds a known compound, it is my expert opinion that while this may sometimes be the case, there are many instances where this is not true and thus this conclusion should not be

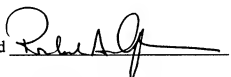
adopted as a general rule. In addition, it is my opinion that one of ordinary skill in the art, being a person with a doctoral degree, 5-10 years of research experience in medicinal chemistry or related fields, and an author of 10 or more peer-reviewed articles, would recognize that in many cases, replacement of a hydrogen atom with a methyl group can have a dramatic effect on the performance of a molecule. For example, the attached article (Glennon et al., J. Med. Chem, 2000. 43. 1011-1018, copy enclosed) teaches that known $5HT_3$ receptors do not readily accommodate a tryptamine 5-methoxy group. For example, 5-methoxy tryptamine (compound 1b in the article), the O-methyl ether of 5-HT (compound 1a in the article, also known as serotonin), is completely devoid of activity at $5\text{-}HT_3$ receptors whereas 1a (serotonin) readily binds to $5\text{-}HT_3$ receptors (see the first paragraph of the Results and Discussion). In other words, the presence or absence of the methyl group, versus H, makes a large difference in the activity of the compound, and this difference would not be obvious to one of skill in the art merely from an examination of the chemical formulas. The differences were observed only when experimental results were obtained. In addition, data obtained in the experiments described in Glennon et al., show other examples of large impacts on activity when changes such as H to methyl are carried out. Compounds 11 and 12 in the table on page 1013 display 5-HT6 receptor affinities (Ki's) of 78 vs 510, respectively. The difference between 11 and 12 is that 11 has H at position R1 whereas the R1 position is methyl in 12. In other words, we have conclusively demonstrated that H is NOT equal to Me in all instances! In my opinion, this data demonstrates and would demonstrate to one of ordinary skill in the art, that small changes in variable groups in a molecule, such as the substitution of H with methyl, can have a significant effect on the activity of a molecule.

5. With specific regards to the present invention, it would not be obvious to one of skill in the art, with a knowledge of Furukawa, Shell, Chiou and Bodor, to use the compounds depicted in Formula I of the present application to treat glaucoma. The compounds of Furukawa differ from those of Shell, Chiou and Bodor and those of the present invention (at least) by not having a methyl group on the ethylamine chain, and Furukawa does not teach the treatment of glaucoma but the treatment of obesity and/or diabetes. The compounds of Shell, Chiou and Bodor differ from those used in the methods of the present invention (at least) by having H *para* to the ethylamine chain, rather than $C_{1\text{-}3}$ alkyl, Cl, Br, or I, as is required in the practice of the present invention. Due to the sensitivity of biological systems, where even small changes in the structure

of a compound can have unpredictable results, one of skill in the art with a knowledge of Furukawa, Shell, Chiou and Bodor would not assume that the compounds used in the methods of the present invention would be useful to treat glaucoma.

6. In addition, with specific regard to the present invention, the experimental results demonstrate that the presence of a methyl on the ethylamine side chain of the compounds utilized in the present invention confers stability to the compounds. These results show that the presence of the methyl group instead of H confers significant metabolic stability on the molecule, which is otherwise susceptible to oxidative deamination by MAO. This provides another example of how a change from H to methyl can have far-reaching, non-obvious effects on the properties of a molecule.

7. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the above-referenced application and any patent issuing thereon.

Date 4/24/09 Signed 

Dr. Richard A. Glennon

# RICHARD A. GLENNON


**PERSONAL INFORMATION**

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|---|---|
| Home Address: | 3810 Reeds Landing Circle<br>Midlothian, Virginia 23113 |
| Office Address: | **554A Smith Building; Department of Medicinal Chemistry<br>School of Pharmacy, Box 980540; Medical College of Virginia Campus<br>Virginia Commonwealth University, Richmond, VA 23298-0540** |
| Phone: | (804)828-8487 |
| Fax: | (804)828-7404 |
| E-mail: | glennon@vcu.edu |


**EDUCATION**

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|---|---|
| Ph.D. 1973: | Medicinal Chemistry; School of Pharmacy,<br>State University of New York; Buffalo, NY |
| M. S. 1969: | Medicinal Chemistry; School of Pharmacy<br>Northeastern University; Boston, MA |
| B. S. 1967: | Pharmacy; Northeastern University; Boston, MA |

**POSTDOCTORAL TRAINING**

Alcohol, Drug Abuse, Mental Health Administration (ADAMHA) Postdoctoral Fellow (Psychopharmacology); Department of Pharmacology and Experimental Therapeutics, School of Medicine; State University of New York: 1973 - 1975.

**PROFESSIONAL POSITIONS**

- Chair, Department of Medicinal Chemistry, VCU, 2006- to date
- Interim Chair, Department of Medicinal Chemistry, VCU, 2005- 2006
- Vice Chair, Department of Medicinal Chemistry, VCU, 1998-2005
- Acting Chair, Department of Medicinal Chemistry, MCV/VCU, 1997
- Associate Dept. Chair, Department of Medicinal Chemistry, School of Pharmacy, VCU; 1990-1996
- Graduate Program Director; Department of Medicinal Chemistry, VCU, 1995- 2007
- Professor, Department of Medicinal Chemistry School of Pharmacy, VCU; 1983- to date
- Affiliate Professor, Department of Pharmacology and Toxicology, School of Medicine; VCU; 1986- to date
- Associate Professor, Department of Medicinal Chemistry, School of Pharmacy, VCU; 1980-1983
- Assistant Professor, Department of Medicinal Chemistry, School of Pharmacy, VCU; 1975-1980
- Research Chemist, Warner-Lambert Research Institute; Morris Plains New Jersey; 1967-1968
- Staff Pharmacist, Bon Secours Hospital, Methuen, MA 1969; Staff Pharmacist, Childrens' Hospital and Medical Center, Boston, Massachusetts 1967 (Pharmacy Intern 1962-1966); Community Pharmacist, Part-time: Boston, MA; Lawrence, MA; Methuen, MA; Brookline, MA. 1967-1969

## HONORS

- School of Pharmacy *Instructor of the Year Award*, 1979
- Virginia Commonwealth University *Distinguished Scholar Award*, 1993
- Aerican Pharmaceutical Association *Research Achievement Award*, 1995
- Virginia Commonwealth University *Laboratory Safety Award* – 2000, 2004, 2006
- Florida A&M University, *Center of Excellence Distinguished Lecturer Award* – 2003
- Virginia Commonwealth University, School of Pharmacy *Instructor of the Year Award*, 2004
- Virginia Commonwealth University, School of Pharmacy *Research Award*, 2005
- Virginia Commonwealth University, *Award of Excellence*, 2004
- European *Order of the Oak and Tulip* award for excellence in receptor medicinal chemistry, 2007

## PUBLICATIONS

More than 400 scientific publications and book chapters

## EDITORIAL BOARD ACTIVITIES

- Senior Editor, *Journal of Medicinal Chemistry*
- Member, Editorial Board of *Pharmacology, Biochemistry & Behavior*
- Member, Editorial Board of *Current Medicinal Chemistry: CNS Agents*
- Member, Editorial Board *Current Topics in Medicinal Chemistry*
- Editor Emeritus and Consultant for *Medicinal Chemistry Research*
- Member, Editorial Board of *Brazilian Journal of Pharmaceutical Sciences*
- Associate Editor of *Journal of Drug Education and Awareness*
- Member, Editorial Board, *Current Chemical Biology*
- Member, Editorial Board, *Medicinal Chemistry Reviews*
- Member, Editorial Board, Burger's Medicinal Chemistry

**PUBLICATIONS**

**1973-1979**


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2. Coburn, R. A.; Glennon, R. A. Synthesis and properties of mesoionic thiazolo[3,2-a]pyrimidin-5,7-diones. *J. Heterocyclic Chem.* **1973**, *10*, 487.
3. Coburn, R. A.; Glennon, R. A. Synthesis and *in vitro* antibacterial properties of mesoionic thiazolo[3,2-a]pyrimidin-5,7-diones and mesoionic 1,3,4-thiadiazolo[3,2a]pyrimidin-5,7-diones. *J. Pharm. Sci.* **1973**, *62*, 1785.
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5. Coburn, R. A.; Glennon, R. A.; Chmielewicz, Z. *In vitro* antibacterial activity of mesoionic 1,3,4-thiadiazolo [3,2a]pyrimidin-5,7-diones. *J. Med. Chem.* **1974**, *17*, 1025.
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7. Glennon, R. A.; Von Strandtmann, M. Cyclodehydration of N-heteroarylcarbamoylmethylbenzamides. *J. Heterocyclic Chem.* **1975**, *12*, 135.
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14. Watson, H.; Glennon, R.A. Common drug interactions. *Anesthesia Update* **1978**, *6*, 1.
15. Glennon, R. A.; Kier, L. B.; Shulgin, A. T. A molecular connectivity analysis of mescaline analogs. *J. Pharm. Sci.* **1979**, *68*, 906.
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17. Glennon, R. A.; Bass, R. G.; Schubert, E. Alkylation of thiazolo[3,2-a]pyrimidin-5,7-diones; *J. Heterocyclic Chem.* **1979**, *16*, 903.
18. Glennon, R. A. The effect of chirality on serotonin receptor affinity. *Life Sciences* **1979**, *24*, 1487.
19. Glennon, R. A. A similarity between rat fundus serotonin receptors and brain serotonin binding sites. *Res. Commun. Psychol. Psychiat. Behav.* **1979**, *4*, 333.
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**1980-1984**


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**1985-1989**

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# 2-Substituted Tryptamines: Agents with Selectivity for 5-HT$_6$ Serotonin Receptors[‖]

Richard A. Glennon,*,[†] Mase Lee,[†] Jagadeesh B. Rangisetty,[†] Malgorzata Dukat,[†] Bryan L. Roth,[‡] Jason E. Savage,[‡] Ace McBride,[‡] Laura Rauser,[‡] Sandy Hufeisen,[‡] and David K. H. Lee[§]

*Department of Medicinal Chemistry, School of Pharmacy, Virginia Commonwealth University, Richmond, Virginia 23298, Departments of Biochemistry, Psychiatry, and Neurosciences, School of Medicine, Case Western Reserve University, Cleveland, Ohio 44106, and Allelix Biopharmaceuticals, Mississauga, Ontario L4V 1V7, Canada*

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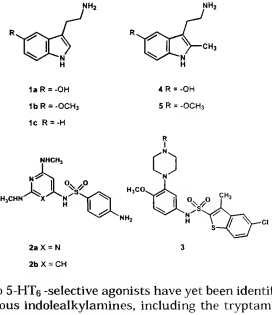
Several 2-alkyl-5-methoxytryptamine analogues were designed and prepared as potential 5-HT$_6$ serotonin agonists. It was found that 5-HT$_6$ receptors accommodate small alkyl substituents at the indole 2-position and that the resulting compounds can bind with affinities comparable to that of serotonin. In particular, 2-ethyl-5-methoxy-*N*,*N*-dimethyltryptamine (**8**) binds with high affinity at human 5-HT$_6$ receptors ($K_i$ = 16 nM) relative to 5-HT ($K_i$ = 75 nM) and was a full agonist, at least as potent (**8:** $K_{act}$ = 3.6 nM) as serotonin ($K_{act}$ = 5.0 nM), in activating adenylate cyclase. Compound **8** displays modest affinity for several other populations of 5-HT receptors, notably h5-HT$_{1A}$ ($K_i$ = 170 nM), h5-HT$_{1D}$ ($K_i$ = 290 nM), and h5-HT$_7$ ($K_i$ = 300 nM) receptors, but is otherwise quite selective. Compound **8** represents the first and most selective 5-HT$_6$ agonist reported to date. Replacing the 2-ethyl substituent with a phenyl group results in a compound that retains 5-HT$_6$ receptor affinity (i.e., **10:** $K_i$ = 20 nM) but lacks agonist character. 2-Substituted tryptamines, then, might allow entry to a novel class of 5-HT$_6$ agonists and antagonists.

## Introduction

Serotonin (5-hydroxytryptamine, 5-HT; **1a**) receptors are classified as belonging to one of several different families: 5-HT$_1$−5-HT$_7$. One of the newest populations identified are the 5-HT$_6$ receptors.[1] 5-HT$_6$ serotonin receptors are members of the G-protein superfamily, are positively coupled to an adenylate cyclase second-messenger system, and are found primarily in the central nervous system.[2] The exact clinical significance of 5-HT$_6$ receptors is unknown at this time. Of interest, however, is that a number of typical and atypical antipsychotic agents and tricyclic antidepressants bind with high affinity at 5-HT$_6$ receptors (i.e., with $K_i$ values of <100 nM).[3−5] In rats prevented from expressing 5-HT$_6$ receptors, the animals behave in a manner that seems to involve an increase in cholinergic function; this has led to speculation that one of the roles of 5-HT$_6$ receptors may be to control cholinergic neurotransmission and that 5-HT$_6$-selective antagonists could be useful in the treatment of anxiety and memory deficits.[6,7] It has been further suggested that GABA-containing neurons in the striatum and glutamate-containing neurons in the hippocampus could be targets of 5-HT actions mediated by 5-HT$_6$ receptors.[8] 5-HT$_6$ ligands might thus be of value in the treatment of anxiety and related disorders. Other studies suggest that 5-HT$_6$ receptors might be involved in motor function, mood-dependent behavior, and early growth processes involving serotonin.[9−11]

Ro 04-6790 (**2a**) and Ro 63-0563 (**2b**) represent the first 5-HT$_6$-selective antagonists.[12] Several related structures have also been reported including SB-271046 (**3**, R = H).[13] Repeated intracerebroventricular administration of antisense oligonucleotides to rats to prevent expression of 5-HT$_6$ receptors produces a behavioral syndrome that consists of yawning, stretching, and chewing;[6,7] administration of Ro 04-6790 and Ro 63-0563 to naive animals produced a similar effect.[12] [$^3$H]Ro 63-0563 has been developed as a radioligand for binding studies.[12b]




No 5-HT$_6$ -selective agonists have yet been identified. Various indoleallkylamines, including the tryptamines

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* Correspondence to: Richard A. Glennon, Ph.D., Box 980540, Department of Medicinal Chemistry, Virginia Commonwealth University, Richmond, VA 23298-0540. Phone: 804-828-8487. Fax: 804-828-7404. E-mail: glennon@hsc.vcu.edu.

[†] Virginia Commonwealth University.

[‡] Case Western Reserve University.

[§] Allelix Biopharmaceuticals.

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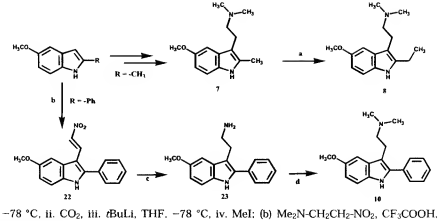
**Scheme 1**[a]



[a] (a) i. *n*BuLi, THF, −78 °C, ii. $CO_2$, iii. *t*BuLi, THF, −78 °C, iv. MeI; (b) $Me_2N$-$CH_2CH_2$-$NO_2$, $CF_3COOH$. (c) $LiAlH_4$, THF, Δ. (d) $NaBH_3CN$, 37% $CH_2O$, MeCN, HOAc.

5-HT (**1a**) and 5-methoxytryptamine (**1b**), and ergolines, such as (+)lysergic acid diethylamide (LSD) and lisuride, bind with high affinity. In fact, [$^{125}$I]iodo-LSD and [$^3$H]LSD have been used to label 5-$HT_6$ receptors. The purpose of our present study was to identify potential agonists with enhanced selectivity for 5-$HT_6$ receptors that might be useful for investigating this population of receptors and receptor function.

5-HT and 5-methoxytryptamine have been demonstrated to act as 5-$HT_6$ agonists and produce a potent dose-dependent increase in cAMP levels.[14] Unfortunately, these tryptamines are notoriously nonselective and bind at multiple populations of 5-HT receptors.[15] It has been demonstrated, however, that with appropriate molecular modification tryptamine derivatives can be developed that display enhanced selectivity for different populations of 5-HT receptors.[15]

We began our investigation by exploring the structure−affinity relationships for the binding of tryptamines at 5-$HT_6$ receptors.[16] We found that O-methylation of 5-HT (**1a**: $K_i$ = 75 nM) to 5-methoxytryptamine (**1b**: $K_i$ = 88 nM) had little effect on affinity and that removal of the hydroxyl group to give tryptamine (**1c**: $K_i$ = 180 nM) only halved affinity.[16] Most other changes led to significant decreases in affinity. For example, lengthening the alkyl chain by one methylene unit, conformational restriction of the side chain as a 1,2,3,4-tetrahydropyrido[3,4-*b*]indole, replacement of the indolic nitrogen atom with an $sp^3$-hybridized carbon atom, and quaternization of the terminal amine all resulted in a dramatic reduction in affinity (i.e., $K_i$ > 5000 nM). On the other hand, N-monomethylation and N,N-dimethylation resulted in retention or a slight increase in affinity. More importantly, we found that introduction of a 2-methyl substituent was tolerated. That is, 2-methyl 5-HT (**4**: $K_i$ = 46 nM) possessed an affinity at least comparable to that of 5-HT itself. This is particularly noteworthy because, with the exception of 5-$HT_3$ receptors, 2-methyl substitution is generally thought to reduce the affinity of tryptamines for most populations of 5-HT receptors. Indeed, 2-methyl 5-HT (**4**) is currently considered a 5-$HT_3$-selective ligand. Interestingly, we have now demonstrated that 2-methyl 5-HT binds at 5-$HT_6$ receptors ($K_i$ = 46 nM) with much higher affinity than it displays for 5-$HT_3$ receptors ($K_i$ = 1200 nM).[16] Given that 2-methylation of 5-HT is tolerated by 5-$HT_6$ receptors and because 2-methyl 5-HT has been previously considered a 5-$HT_3$-selective agent, this seemed to be a suitable starting point for the exploration of potentially selective 5-$HT_6$ agents.

## Chemistry

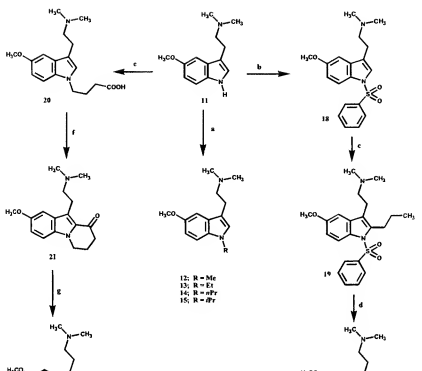
The 2-methyl derivative **7** was prepared via a literature procedure[17] from 2-methylindole using the Speeter−Anthony method, and the 2-ethyl homologue **8** was prepared by treatment of the free base of **7** with *t*BuLi followed by the addition of MeI (Scheme 1). The 2-phenyl derivative **10** was prepared from 5-methoxy-2-phenylindole as shown in Scheme 1. Reaction of 5-methoxy-2-phenylindole with *N*,*N*-dimethylamino-2-nitroethylene afforded the nitrovinyl derivative **22**; compound **22** was reduced to amine **23** using $LiAlH_4$, and the amine was reductively methylated with formaldehyde and sodium cyanoborohydride.

Many of the 5-methoxy-substituted tryptamines were prepared from 5-methoxy-*N*,*N*-dimethyltryptamine (free base of **11**) (Scheme 2). Direct alkylation of **11** (free base) under basic conditions with the appropriate alkyl halide provided the $N_1$-substituted derivatives **12**−**15**. The procedure is exemplified for compound **15**. The 2-*n*-propyl homologue **9** was also obtained from **11** (Scheme 2). The $N_1$-position of **11** (free base) was protected with a benzenesulfonyl group, and the resulting compound, **18**, was treated with *n*PrI to give **19**; hydrolysis of the protecting group provided compound **9**. Reaction of the indolyl anion of **11** (free base) with anhydrous γ-butyrolactone afforded the *N*-butyrate **20**. Attempts to cyclize **20** using PPA at 100 °C were unsuccessful and resulted in decomposition; however, substitution of PPE[18] for PPA gave the desired **21**, which was reduced with borane to give the desired **16** (Scheme 2). Compound **17** was synthesized via debenzylation of its known *N*-benzyl derivative.[19]

## Results and Discussion

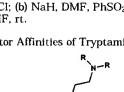
2-Methyl 5-HT (**4**) is currently considered a 5-$HT_3$-selective ligand; on the other hand, it is known that 5-$HT_3$ receptors do not readily accommodate a tryptamine 5-methoxy group. For example, 5-methoxytryptamine (**1b**), the *O*-methyl ether of 5-HT (**1a**), is completely devoid of activity at 5-$HT_3$ receptors.[20] Hence, the first compound that we examined was the simple 2-methyl

**Scheme 2**[a]




[a] (a) NaH, DMF, rt, and $Me_2SO_4$, EtBr, *n*PrCl or *i*PrCl; (b) NaH, DMF, $PhSO_2Cl$, rt; (c) BuLi, DME, *n*PrI, −10 °C; (d) Mg, MeOH, rt; (e) γ-butyrolactone; (f) PPE, $CHCl_3$, reflux; (g) $B_2H_6$/THF, rt.

**Table 1.** Physicochemical Properties and 5-$HT_6$ Receptor Affinities of Tryptamine Analogues



| compd | R | $R_5$ | $R_2$ | $R_1$ | yield (%) | RS[a] | mp (°C) | 5-$HT_6$ affinity[b] $K_i$ (nM) | empirical formula[c] |
|---|---|---|---|---|---|---|---|---|---|
| **4** | H | OH | $CH_3$ | H | | | | 46[f] | |
| **5** | H | $OCH_3$ | $CH_3$ | H | | | | 98 | |
| **6** | $CH_3$ | H | $CH_3$ | H | 88 | EtOH−$Et_2O$ | 208 | 300 | $C_{13}H_{18}N_2$·HCl |
| **7** | $CH_3$ | $OCH_3$ | $CH_3$ | H | 92 | A | 242−245 dec | 80 | $C_{14}H_{20}N_2O$·$C_2H_2O_4$ |
| **8** (EMDT) | $CH_3$ | $OCH_3$ | $C_2H_5$ | H | 16 | B−$Et_2O$ | 123 | 52 | $C_{15}H_{22}N_2O$·$C_4H_4O_4$ |
| **9** | $CH_3$ | $OCH_3$ | *n*$C_3H_7$ | H | 45 | A | 146−147 | 185 | $C_{16}H_{24}N_2O$·$C_2H_2O_4$[d] |
| **10** | $CH_3$ | $OCH_3$ | $C_4H_6$ | H | 25 | A | 187−188 | 54 | $C_{19}H_{22}N_2O$·$C_2H_2O_4$ |
| **11** | $CH_3$ | $OCH_3$ | H | H | | | | 78 | |
| **12** | $CH_3$ | $OCH_3$ | H | $CH_3$ | 65 | A | 181−182 | 510 | $C_{14}H_{20}N_2O$·$C_2H_2O_4$ |
| **13** | $CH_3$ | $OCH_3$ | H | $C_2H_5$ | 22 | A | 160−161 | 240 | $C_{15}H_{22}N_2O$·1.5$C_2H_2O_4$ |
| **14** | $CH_3$ | $OCH_3$ | H | *n*$C_3H_7$ | 93 | A−$Et_2O$ | 104 | 200 | $C_{16}H_{24}N_2O$·$C_4H_4O_4$ |
| **15** | $CH_3$ | $OCH_3$ | H | *i*$C_3H_7$ | 49 | A−$Et_2O$ | 101 | 130 | $C_{16}H_{24}N_2O$·$C_4H_4O_4$ |
| **16** | $CH_3$ | $OCH_3$ | $-CH_2CH_2CH_2CH_2-$ | | 75 | A | 114−115 | 1030 | $C_{17}H_{24}N_2O$·1.15$C_2H_2O_4$[e] |
| **17** | | | | | 37 | EtOH−$Et_2O$ | 224−226 | 168 | $C_{16}H_{22}N_2O$·$C_2H_2O_4$ |

[a] Recrystallization solvents; EtOH represents absolute ethanol; $Et_2O$, anhydrous ether; A, acetone; B, ethyl acetate. [b] $K_i$ values represent replicate determinations and SEM are ±25%; for purpose of comparison, clozapine was determined to possess a $K_i$ = 5.3 (±0.4) nM. [c] All compounds analyzed correctly to within 0.4% of theory for C, H, and N except where noted. [d] Crystallized with 0.7 mol of $H_2O$. [e] Crystallized with 1 mol of $H_2O$. [f] $K_i$ value previously reported;[16] included for purpose of comparison.

analogue of 5-methoxytryptamine (**1b**: $K_i$ = 88 nM),[16] namely, 5-methoxy-2-methyltryptamine (**5**). Compound **5** ($K_i$ = 98 nM; Table 1) was found to bind at 5-$HT_6$ receptors with an affinity comparable to that of 5-methoxytryptamine. It was also found that **5** lacks affinity for 5-$HT_3$ receptors ($K_i$ > 10000 nM). Compound **5** might be a useful 5-$HT_6$ ligand; however, given that **5** possesses a primary amine, its utility for future in vivo studies might be hampered by its reduced ability to penetrate the blood−brain barrier and/or due to its potential for rapid metabolism by oxidative deamination. To address these problems, we sought to prepare

**Table 2.** Binding Profile of Compounds **7**, **8**, and **10**[a]

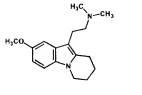
| receptor population | $K_i$, nM (±SEM) | | | |
|---|---|---|---|---|
| | **7** | **8** (EMDT) | **10** | control (agent and $K_i$) |
| NET | 6380 (±3190) | >10000 | >10000 | nortriptyline 6.3 ± 1.2 |
| SERT | >10000 | >10000 | 4700 (±1550) | fluoxetine 3.5 ± 0.7 |
| h5-$HT_{1A}$ | 200 (±60) | 170 (±54) | 1470 (±310) | WAY 100,635 0.6 ± 1.5 |
| h5-$HT_{1D}$ | 250 (±180) | 290 (±70) | 6225 (±70) | ergotamine 0.8 ± 0.6 |
| h5-$HT_{1E}$ | 1800 (±600) | 520 (±180) | >10000 | serotonin 0.5 ± 0.15 |
| r5-$HT_{2A}$ | >10000 | >10000 | 470 (±10) | clozapine 9 ± 1 |
| r5-$HT_{2C}$ | 4020 (±640) | 1810 (±490) | 675 (±180) | clozapine 23 ± 5 |
| h5-$HT_{5A}$ | 10450 (±2195) | 4620 (±650) | 5160 (±930) | ergotamine 22 ± 3 |
| h5-$HT_7$ | 145 (±34) | 300 (±60) | 155 (±35) | clozapine 9 ± 2 |
| h5-$HT_6$ | 60 (13) | 16 (±4) | 20 (±5) | clozapine 10 ± 3 |

[a] Compounds displayed $K_i$ values of >10000 nM at the following populations of receptors: histamine, NMDA, PCP, acetylcholine, opiate, and vasopressin receptors; see Experimental Section for specific subpopulations examined. $K_i$ values were >10000 nM for compounds **7** and **8** at $hD_1$, $rD_2$, $rD_3$, $rD_4$, and $hD_5$ receptors and >10000 nM for **10** at $hD_1$, $rD_2$, and $rD_4$ receptors; although **10** produced 70% inhibition at 10000 nM at $rD_3$ and $hD_5$ receptors, it was not further evaluated. NET and SERT represent the norepinephrine and serotonin transporters. $K_i$ values for all three compounds at the dopamine transporter were >10000 nM.

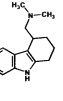
several related derivatives that were somewhat more lipophilic and/or that might be less prone to metabolism.

One approach to enhancing lipophilicity and hindering metabolism was to add *N*,*N*-dimethyl substituents to the terminal amine; a second approach to enhancing lipophilicity was to homologate the 2-position substituent. 2-Methyl-*N*,*N*-dimethyltryptamine (2-methyl DMT, **6**: $K_i$ = 300 nM), an *N*,*N*-dimethyl analogue of **5** lacking the 5-methoxy group, binds with severalfold lower affinity than **5** itself. Reintroduction of the 5-methoxy group, affording 2-methyl-5-methoxy DMT (**7**: $K_i$ = 80 nM), enhanced affinity. Homologation of the 2-methyl substituent to an ethyl group (i.e., **8**: $K_i$ = 52 nM) resulted in a slight increase in affinity and in a compound with affinity at least comparable to that of 5-HT itself. Further homologation of the ethyl substituent to a 2-*n*-propyl group (i.e., **9**: $K_i$ = 185 nM) reversed this trend. To explore the possibility of bulk tolerance, we examined the 2-phenyl derivative **10** ($K_i$ = 54 nM) and found it to bind with an affinity comparable to that of **8**.

Another attempt to enhance lipophilicity was to incorporate small alkyl substituents at the indole $N_1$-position. The idea was to subsequently incorporate a 2-alkyl substituent into whatever $N_1$-substituted analogue retained high 5-$HT_6$ receptor affinity. $N_1$-Methylation of 5-methoxy DMT (**11**: $K_i$ = 78 nM) decreased 5-$HT_6$ receptor affinity of the resulting compound by >6-fold (**12**: $K_i$ = 510 nM). Homologation of the $N_1$-methyl group to an ethyl group (i.e., **13**: $K_i$ = 240 nM) or *n*-propyl group (i.e., **14**: $K_i$ = 200 nM) doubled affinity, but the compounds did not bind as well as **11**. Branching of **13** to the isopropyl derivative **15** ($K_i$ = 130 nM) resulted in a further slight enhancement of affinity. However, none of these compounds displayed significantly enhanced affinity. Compound **16** ($K_i$ = 1030 nM), which may be viewed as a cyclic 1,2-disubstituted analogue of **11**, was also prepared for evaluation and was found to bind with reduced affinity.




16




17

In a final attempt to enhance lipophilicity in the 2-substituted DMT series, the propyl group of **9** was tethered to the DMT side chain to afford **17**; compound **17** ($K_i$ = 168 nM) was found to bind at 5-$HT_6$ receptors with about 3-fold lower affinity than **8**. Although compound **17** possesses an asymmetric center and can exist as a pair of optical isomers, no attempt was made to examine the individual isomers because structurally related agents have been shown to bind at 5-$HT_{1D}$ receptors,[21,22] and it was anticipated that the isomers of **17** might lack the desired selectivity.

**Binding Profile.** Compounds **7**, **8**, and **10** were selected for examination of detailed binding profiles. All three agents were examined at more than 30 different receptor populations and produced <50% inhibition of binding at a concentration of 10000 nM at most of these populations. Where >50% displacement was observed, $K_i$ values were determined (Table 2). For these studies, $K_i$ values were redetermined for **7**, **8**, and **10**. Compounds **8** and **10** bind at human 5-$HT_6$ receptors with comparable affinity ($K_i$ = 16 and 20 nM, respectively) and with an affinity similar to that of clozapine; compound **7** binds with severalfold lower affinity ($K_i$ = 60 nM). Although **7** and **8** appear relatively selective, they also bind at h5-$HT_{1A}$, h5-$HT_{1D}$, h5-$HT_{1E}$, and h5-$HT_7$ receptors, yet compound **8**, in particular, still displays 10-fold selectivity over 5-$HT_{1A}$ receptors and nearly 20-fold selectivity over h5-$HT_{1D}$ and h5-$HT_7$ receptors. Compound **10** is more selective and displays 735-fold selectivity over h5-$HT_{1A}$ receptors and >300-fold selectivity over h5-$HT_{1D}$ receptors.

**Functional Studies.** Compounds **7**, **8**, and **10** were examined for their ability to activate adenylate cyclase. Whereas compounds **7** and **8** behaved as full agonists ($K_{act}$ = 7.9 ± 5.0 and 3.6 ± 1.3 nM, respectively) relative to 5-HT ($K_{act}$ = 5.0 ± 3.0 nM), compound **10** showed no agonist activity (see Figure 1). Compound **10** inhibited 5-HT-stimulated adenylate cyclase at 10000 nM suggesting that it is an antagonist.

## Summary

Molecular manipulation of a tryptamine template revealed that 2-methyl substitution was tolerated by 5-$HT_6$ receptors.[16] Because 2-methyl 5-HT was previously considered to be a 5-$HT_3$-selective ligand and by taking advantage of the fact that 5-$HT_3$ receptors do not readily accommodate a 5-methoxy group, a series of

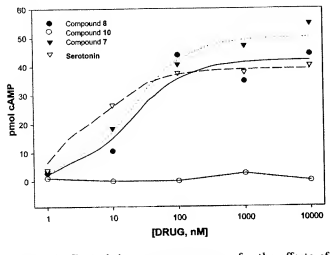



**Figure 1.** Typical dose−response curves for the effects of compounds **7**, **8**, and **10** as 5-$HT_6$ agonists in an adenylate cyclase assay; serotonin was used as control. Each compound was examined at five concentrations.

2-alkyl-5-methoxytryptamines was synthesized for evaluation at 5-$HT_6$ receptors. Several compounds were identified with affinities at least comparable to that of 5-HT itself ($K_i$ = 75 nM). In particular, 2-ethyl-5-methoxy-*N*,*N*-dimethyltryptamine (EMDT; **8**) possessed high affinity ($K_i$ = 16 nM) and displayed reasonable selectivity for 5-$HT_6$ versus other receptors examined. In functional studies, EMDT (**8**) was demonstrated to behave as a 5-$HT_6$ agonist ($K_{act}$ = 3.6 nM) with a potency at least equivalent to that of 5-HT ($K_{act}$ = 5.0 nM). EMDT is the most selective 5-$HT_6$ agonist reported to date. Also of interest is the 2-phenyl derivative **10** (MPDT: $K_i$ = 20 nM), which possesses a somewhat different binding profile than **8**; compound **10** lacks agonist activity up to concentrations of 10000 nM and may represent a novel 5-$HT_6$ antagonist. Indeed, when examined at the single concentration of 10000 nM, **10** behaved an antagonist. Hence, with the appropriate substituents, 2-substituted tryptamines may provide entry to new 5-$HT_6$-selective agonists and antagonists.

## Experimental Section

**Synthesis.** Melting points, determined with a Thomas-Hoover melting point apparatus, are uncorrected. Proton magnetic resonance spectra were obtained with a GE QE-300 or Varian Gemini 300 spectrometer; and tetramethylsilane was used as an internal standard. Infrared spectra were recorded on a Nicolet 5ZDX FT-IR. Elemental analysis was performed by Atlantic Microlab Inc. and determined values are within 0.4% of theory. Flash chromatography was performed on silica gel (Merck grade 60, 230−400 mesh 60 Å). Certain compounds were previously reported in the literature but due to difficulty in either preparing or purifying the reported salt, a different salt was prepared. Specifically, compounds **7**,[17] **10**,[23] and **12**[24] are known as their HCl salts but were isolated as their monooxalate salts in the present investigation. Compound **6**, prepared earlier as a maleate salt,[25] was isolated as its HCl salt. All four of these compounds analyzed correctly for C, H, and N.

**2-Ethyl-5-methoxy-*N*,*N*-dimethyltryptamine Maleate (8).** A 2.5 M solution of *n*BuLi (1.75 mL, 4.38 mmol) was added in a dropwise manner to a stirred solution of **7**[17] (free base) (1.00 g, 4.33 mmol) in dry THF (7 mL) at −78 °C under $N_2$. After stirring the reaction mixture for 5 min, the cooling bath was removed and $CO_2$ gas was passed into the solution for 10 min. The solvent was removed at 0 °C under reduced pressure to give a transparent solid. The flask was flushed with $N_2$ and dry THF (7 mL) was added. The reaction mixture was degassed at −150 °C under reduced pressure of 1 mmHg, then allowed to warm to −78 °C; 1.7 M *t*BuLi (2.8 mL, 4.8 mmol) was added to give a bright yellow solution. The cooling bath was replaced by an ice-salt bath and the reaction was kept at −20 °C for 45 min, then cooled to −78 °C, and MeI (0.3 mL, 4.81 mmol) was added in a dropwise manner. The solution was kept at −78 °C for 3 h. The reaction mixture was acidified with a saturated ethereal solution of HCl. Anhydrous $Et_2O$ was added to the resulting suspension and the supernatant was decanted. The residue was heated at 100 °C under reduced pressure for 20 min. The resulting residue was purified by flash chromatography on silica gel ($CH_2Cl_2$/MeOH; 12:1) to give 0.17 g of a bright yellow oil (16%): $^1$H NMR ($CDCl_3$) $\delta$ 8.06 (s, 1H), 7.14 (d, 1H, $J$ = 8.67 Hz), 6.98 (s, 1H), 6.76 (dd, 1H, $J$ = 2.34, 8.73 Hz), 3.84 (s, 3H), 2.91−2.87 (m, 2H), 2.71 (q, 2H, $J$ = 7.38 Hz), 2.57−2.52 (m, 2H), 2.38 (s, 6H). 1.25 (t, 3H, $J$ = 7.38 Hz). The maleate salt was prepared and recrystallized from an $EtOAc/Et_2O$ mixture: mp 123 °C. Anal. ($C_{15}H_{22}N_2O{\cdot}C_4H_4O_4$) C, H, N.

**5-Methoxy-2-*n*-propyl-*N*,*N*-dimethyltryptamine Oxalate (9).** Magnesium turnings (840 mg) and $NH_4Cl$ (77 mg, 1.44 mmol) were added to a solution of **19** (free base) (259 mg, 0.65 mmol) in MeOH (17 mL) and the mixture was allowed to stir at room temperature for 1 h. Saturated $NH_4Cl$ solution was added and the reaction mixture was extracted with $CH_2Cl_2$. The organic portion was dried ($MgSO_4$) and the solvent was removed under reduced pressure. The residue was purified by flash chromatography on silica gel ($CH_2Cl_2$/MeOH; 9:1) to give 75 mg (45%) of a bright yellow oil: $^1$H NMR ($CDCl_3$) $\delta$ 7.71 (brs, 1H), 7.16 (d, 1H, $J$ = 8.67 Hz), 6.99 (d, 1H, $J$ = 2.43 Hz), 6.77 (dd, 1H, $J$ = 2.25, 8.73 Hz), 3.85 (s, 3H). 2.89−2.83 (m, 2H), 2.69 (t, 2H, $J$ = 7.56 Hz), 2.53−2.47 (m, 2H), 2.36 (s, 6H), 1.68 (tq, 2 H, $J$ = 7.28, 7.56 Hz), 0.98 (t, 3H, $J$ = 7.28 Hz). The oxalate salt was prepared and recrystallized from acetone: mp 146−147 °C. Anal. ($C_{16}H_{24}N_2O{\cdot}C_2H_2O_4{\cdot}0.7H_2O$) C, H, N.

**5-Methoxy-2-phenyl-*N*,*N*-dimethyltryptamine Oxalate (10).** 5-Methoxy-2-phenylindole[26] (3 g, 13.44 mmol) was added to a stirred ice-cooled solution of 1-dimethylamino-2-nitroethylene (1.56, 13.44 mmol) in trifluoroacetic acid (8 mL). The resulting mixture was allowed to stir under $N_2$ at room temperature for 30 min and was then poured into ice/water. The solution was extracted with EtOAc and the organic portion was washed consecutively with saturated $NaHCO_3$ solution, $H_2O$, then brine. The organic portion was dried ($MgSO_4$) and solvent was removed under reduced pressure. The residue was recrystallized from $CH_2Cl_2$/hexane to give 2.36 g (60%) of **22** as a red powder: $^1$H NMR (acetone-$d_6$) $\delta$ 8.82 (brs, 1H), 8.32 (d, 1H, $J$ = 13.44 Hz), 7.94 (d, 1H, $J$ = 13.35 Hz), 7.69−7.41 (m, 7H), 6.98−6.94 (m, 1H), 3.92 (s, 3H); IR (KBr) 1606, 1475, 1251 cm$^{-1}$. A solution of **22** (2.00 g, 6.75 mmol) in dry THF (20 mL) was added in a dropwise manner to a cooled (0 °C) suspension of $LiAlH_4$ (1.54 g, 40.5 mmol) in dry THF (40 mL) under $N_2$. The reaction mixture was heated at reflux for 1 h and then allowed to stand at room-temperature overnight. The resulting mixture was quenched with $H_2O$ then 15% NaOH solution. Celite was added and the solution was filtered. The solvent was removed under reduced pressure. The residue was purified by flash chromatography on silica gel ($CH_2Cl_2$/MeOH; 9:1) to give 1.00 g (55%) of the primary amine **23**[23] as an oil: $^1$H NMR ($CDCl_3$) $\delta$ 8.19 (brs, 1H), 7.59−7.58 (m, 2H), 7.49−7.44 (m, 2H), 7.39−7.34 (m, 1H), 7.28−7.25 (m, 1H), 7.09 (d, 1H, $J$ = 2.37 Hz), 6.88 (dd, 1H, $J$ = 2.24, 8.75 Hz), 3.89 (s, 3H), 3.04 (brs, 4H); IR (KBr) 3397, 3347 cm$^{-1}$. Sodium cyanoborohydride (510 mg, 8.12 mmol) was added to a solution of primary amine **23** (700 mg, 2.63 mmol) and 37% aqueous $CH_2O$ in MeCN (10 mL) at room temperature. The resulting mixture was adjusted to pH 5 with HOAc and was allowed to stir at room-temperature overnight. A 15% solution of NaOH was added to neutralize the mixture and the mixture was extracted with $CH_2Cl_2$. The combined organic portion was washed with saturated $NaHCO_3$ solution and brine. The

organic portion was dried ($MgSO_4$ and solvent was removed under reduced pressure. The residue was purified by flash chromatography on silica gel ($CH_2Cl_2$/MeOH; 9:1) to give 195 mg (25%) of **10** (free base) as a white powder: $^1H$ NMR ($CDCl_3$) $\delta$ 8.05 (brs, 1H), 7.56–7.53 (m, 2H), 7.49–7.44 (m, 2H), 7.39–7.34 (m, 1H), 7.29–7.25 (m, 1H), 7.11 (d, 1H, $J$ = 2.25 Hz), 6.87 (dd, 1H, $J$ = 2.52, 8.73 Hz), 3.89 (s, 3H), 3.13–3.08 (m, 2H), 2.72–2.66 (m, 2H), 2.39 (s, 6H). Although the HCl salt has been previously reported,[23] difficulties in its purification led to isolation of the product as its oxalate salt: mp 187–188 °C after recrystallization from acetone. Anal. ($C_{19}H_{22}N_2O\cdot C_2H_2O_4$) C, H, N.

**5-Methoxy-1-(2-propyl)-*N*,*N*-dimethyltryptamine Maleate (15).** A mixture of 5-methoxy-*N*,*N*-dimethyltryptamine (**11**; free base) (500 mg, 2.29 mmol) and 60% NaH (100 mg, 2.52 mmol) was heated at 100 °C under $N_2$ until evolution of $H_2$ gas ceased. The resultant mass was dissolved in anhydrous DMF (3 mL) and 2-bromopropane (0.25 mL, 2.84 mmol) was added to the solution at 0 °C. The reaction mixture was allowed to stir at room temperature for 3 h. Brine was added and the reaction mixture was extracted with $CH_2Cl_2$. The organic portion was dried ($MgSO_4$) and the solvent was removed under reduced pressure. The residue was purified by flash chromatography on silica gel ($CH_2Cl_2$/MeOH; 10:1) to give 294 mg of a bright yellow oil (49%): $^1H$ NMR ($CDCl_3$) $\delta$ 7.23 (d, 1H, $J$ = 8.94 Hz), 7.04 (d, 1H, $J$ = 2.46 Hz), 7.01 (s, 1H), 6.86 (dd, 1H, $J$ = 2.46, 8.88 Hz), 4.59–4.54 (m, 1H), 3.86 (s, 3H), 2.95–2.89 (m, 2H), 2.66–2.61 (m, 2H), 2.36 (s, 6H), 1.48 (d, 6H, $J$ = 6.72 Hz). The maleate salt was prepared and recrystallized from an acetone/$Et_2O$ mixture: mp 101–102 °C. Anal. ($C_{16}H_{24}N_2O\cdot C_4H_4O_4$) C, H, N.

$^1H$ NMR data for compounds **13** and **14** are as follows: **13** ($CDCl_3$) $\delta$ 7.22 (d, 1H, $J$ = 9.0 Hz), 7.06 (d, 1H, $J$ = 2.5 Hz), 6.95 (s, 1H), 6.88 (dd, 1H, $J$ = 2.5, 9.0 Hz), 4.61 (q, 2H, $J$ = 7.5 Hz), 3.88 (s, 3H), 3.01–2.97 (m, 2H), 2.76–2.73 (m, 2H), 2.45 (s, 6H), 1.44 (t, 3H, $J$ = 7.5 Hz); **14** ($CDCl_3$) $\delta$ 7.19 (d, 1H, $J$ = 8.85 Hz), 7.04 (d, 1H, $J$ = 2.37 Hz), 6.90 (s, 1H), 6.87–6.83 (m, 1H), 3.98 (t, 2 H, $J$ = 7.08 Hz), 3.86 (s, 3H), 2.93–2.87 (m, 2H), 2.64–2.59 (m, 2H), 2.35 (s, 6H), 1.82 (q, 3H, $J$ = 7.2 Hz), 0.91 (t, 2H, $J$ = 7.4 Hz).

**6,7,8,9-Tetrahydro-2-methoxy-10-(*N*,*N*-dimethylaminoethyl)pyrido[1,2-*a*]indole Oxalate (16).** A solution of 1.0 M borane/THF (2 mL, 2 mmol) was added in a dropwise manner to ice-bath cooled **21** (290 mg, 1.01 mmol) under $N_2$. The reaction mixture was allowed to stir at room temperature for 2 h. Acetone (3 mL) was added, and the reaction mixture was heated at reflux for 1 h to quench the unreacted borane reagent. The solvent was removed under reduced pressure. A 15% solution of NaOH was added and the mixture was extracted with $CH_2Cl_2$, and the $CH_2Cl_2$ portion was washed with $H_2O$, then brine. Solvent was removed under reduced pressure. The residue was purified by flash chromatography on silica gel (hexane/EtOAc; 4:1) to give 207 mg (75%) of a light yellow oil: $^1H$ NMR (DMSO-$d_6$) $\delta$ 7.34 (d, 1 H, $J$ = 8.85 Hz), 7.21 (s, 1H), 7.11 (s, 1H), 4.08 (t, 2H, $J$ = 6.65 Hz), 3.79 (s, 3H), 3.40–3.35 (m, 2H), 3.30–3.25 (m, 2H), 3.06–3.01 (m, 2H), 2.83 (s, 6H), 1.76–1.69 (m, 2H), 1.40–1.31 (m, 2H). A small portion was converted to its oxalate salt: mp 114–115 °C. Anal. ($C_{17}H_{24}N_2O\cdot 1.15C_2H_2O_4\cdot H_2O$) C, H, N.

**4-(Dimethylaminomethyl)-6-methoxy-1,2,3,4-tetrahydrocarbazole Oxalate (17).** Sodium metal (1.0 g) was added portionwise over a 30-min period to a stirred solution of 4-(dimethylaminomethyl)-9-benzyl-6-methoxy-1,2,3,4-tetrahydrocarbazole hydrochloride[19] (4.0 g, 0.01 mol) in liquid $NH_3$ (300 mL). $NH_4Cl$ (3.0 g) was added until the blue color of the mixture dissipated. The $NH_3$ was evaporated, $H_2O$ (50 mL) was added, and the mixture was extracted with $CH_2Cl_2$ (3 × 50 mL). The combined organic portion was washed with $H_2O$ (50 mL), brine (50 mL), dried ($MgSO_4$) and evaporated to give an oil. The oil was purified by column chromatography ($CHCl_3$/MeOH; 9:1) and converted to an oxalate salt. The oxalate salt was recrystallized from anhydrous $Et_2O$/absolute EtOH to give 1.8 g (37%) of the desired target as a white powder: mp 224–226 °C; $^1H$ NMR ($CDCl_3$, free base) $\delta$ 8.10 (s, 1H, NH), 7.20 (t, 1H, ArH), 6.90 (d, 1H, ArH), 6.70 (dd, 1H, ArH), 3.80 (s, 3H, $OCH_3$), 3.40 (t, 1H, CH), 3.15 (d, 1H, CH), 3.00 (t, 1H, CH), 2.82 (s, 6H, 2× $CH_3$), 2.63–2.73 (m, 2H, $CH_2$), 2.33 (m, 1H, CH), 1.8–2.0 (m, 3H, $CH_2$-CH). Anal. ($C_{16}H_{22}N_2O\cdot C_4H_2O_4\cdot C$, H, N.

**1-Benzenesulfonyl-5-methoxy-*N*,*N*-dimethyltryptamine Oxalate (18).** A mixture of 5-methoxy-*N*,*N*-dimethyltryptamine (**11**; free base) (4.35 g, 19.93 mmol) and 60% NaH (0.87 g, 21.75 mmol) was heated at 100 °C under $N_2$ until evolution of $H_2$ gas ceased. The resultant mass was dissolved in anhydrous DMF (21 mL) and benzenesulfonyl chloride (2.8 mL, 21.94 mmol) was added in a dropwise manner at 0 °C. The reaction mixture was allowed to stir at room-temperature overnight. Saturated $NaHCO_3$ solution was added and the mixture was extracted with $CH_2Cl_2$. The organic portion was dried ($MgSO_4$ and the solvent was removed under reduced pressure. The residue was purified by flash chromatography on silica gel ($CH_2Cl_2$/MeOH; 9:1) to give 4.39 g of an oil (61%): $^1H$ NMR ($CDCl_3$) $\delta$ 7.89–7.87 (m, 1H), 7.83 (d, 2H, $J$ = 8.0 Hz), 7.51 (t, 1H, $J$ = 7.8 Hz), 7.34 (s, 1H), 6.93–6.92 (m, 2H), 3.82 (s, 3H), 2.80 (t, 2H, $J$ = 7.8 Hz), 2.59 (t, 2H, $J$ = 7.8 Hz), 2.33 (s, 6H); IR ($CHCl_3$) 1357, 1115 $cm^{-1}$. The oxalate salt was prepared and recrystallized from an acetone/$Et_2O$ mixture: mp 224–226 °C. Anal. ($C_{19}H_{22}N_2O_3S\cdot C_2H_2O_4$) C, H, N.

**1-Benzenesulfonyl-5-methoxy-2-*n*-propyl-*N*,*N*-dimethyltryptamine Oxalate (19).** A 2.5 M solution of *n*BuLi (1.4 mL, 3.5 mmol) was added in a dropwise manner to a stirred solution of **18** (free base) (1.00 g, 2.79 mmol) in DME (4 mL) at −10 °C under $N_2$. The resulting solution was allowed to stir for an additional 10 min at −10 °C, and then *n*PrI (0.35 mL, 3.59 mmol) was added. The reaction mixture was allowed to stir for 1 h at −10 °C. Saturated $NaHCO_3$ solution was added and the reaction mixture was extracted with $CH_2Cl_2$. The organic portion was washed with brine and dried ($MgSO_4$); the solvent was removed under reduced pressure and the residue was purified by flash chromatography on silica gel ($CH_2Cl_2$/MeOH; 30:1) to give 0.19 g (17%) of a bright yellow oil: $^1H$ NMR ($CDCl_3$) $\delta$ 8.06 (d, 1H, $J$ = 8.79 Hz), 7.62 (d, 2H, $J$ = 8.22 Hz), 7.51–7.46 (m, 1H), 7.38–7.33 (m, 2H), 6.95 (brs, 1H), 6.89–6.85 (m, 1H), 3.85 (s, 3H), 2.96–2.89 (m, 4H), 2.63–2.57 (m, 2H), 2.48 (s, 6H), 1.73 (q, 2H, $J$ = 7.51 Hz), 1.00 (t, 3H, $J$ = 7.51 Hz); IR ($CHCl_3$) 1355 $cm^{-1}$. The oxalate salt was prepared and recrystallized from acetone: mp 175–176 °C. Anal. ($C_{22}H_{28}N_2O_3S\cdot C_2H_2O_4$) C, H, N.

**6,7,8,9-Tetrahydro-2-methoxy-10-(*N*,*N*-dimethylaminoethyl)pyrido[1,2-*a*]indol-9-one Oxalate (21).** A mixture of 5-methoxy-*N*,*N*-dimethyltryptamine (**11**; free base) (2.00 g, 9.17 mmol) and 60% NaH (0.41 g, 10.1 mmol) was heated at 100 °C under $N_2$ until evolution of $H_2$ gas ceased. The resultant mass was dissolved in anhydrous DMF (25 mL) and anhydrous γ-butyrolactone (1.4 mL, 18.2 mmol) was added in a dropwise manner at room temperature. The reaction mixture was heated at reflux for 20 h, cooled to 0 °C, and acidified by the addition of a saturated ethereal solution of HCl. Additional $Et_2O$ was added to the resulting suspension and the supernatant was decanted. The residue was dissolved in PPE (52.5 mL) and $CHCl_3$ (100 mL) and the reaction mixture was heated at reflux for 3 h under $N_2$. The resulting mixture was neutralized by the addition of 15% NaOH solution, at ice-bath temperature, and extracted with $CH_2Cl_2$. The organic portion was dried ($MgSO_4$) and solvent was removed under reduced pressure. The residue was purified by flash chromatography on silica gel ($CH_2Cl_2$/MeOH; 20:1) to give 0.52 g (20%) of **21** (free base) as a yellow oil: $^1H$ NMR (DMSO-$d_6$) $\delta$ 7.35 (d, 1H, $J$ = 8.79 Hz), 7.18 (s, 1H), 6.88 (d, 1H, $J$ = 8.85 Hz), 4.06 (t, 2H, $J$ = 6.60 Hz), 3.80 (s, 3H), 3.42–3.36 (m, 2H), 3.17–3.12 (m, 2H), 2.85 (s, 6H), 2.66–2.62 (m, 2H); IR ($CHCl_3$) 1648 $cm^{-1}$. A small sample was converted to the oxalate salt: mp 191–192 °C dec. Anal. ($C_{19}H_{24}N_2O_2\cdot 1.6C_2H_2O_4$) C, H, N.

**5-HT$_6$ Radioligand Binding Assay.** The binding assay employed human 5-HT$_6$ receptors stably transfected to HEK 293 human embryonic kidney cells with [$^3$H]lysergic acid diethylamide (70 Ci/mmol; DuPont NEN) as radioligand. All

assays were conducted in triplicate using polypropylene 1 mL/well plates (Anachemia). The radioligand was diluted in incubation buffer in borosilicate glass vials and protected from light. Competing agents (1 mM stock solutions) were dissolved in DMSO or saline and stored at −20 °C in 1.2-mL polypropylene tubes (ElKay). Dilutions of compounds were made using incubation buffer in 96-well polypropylene plates and mixed by multichannel pipetting > 25 times. Serial dilutions (1 in 4) started at a final concentration of 10000 nM. Final concentrations > 10000 nM were individually prepared from the 1 mM stock solution. Nonspecific binding was defined by 100 μM serotonin creatinine sulfate (Research Biochemicals) prepared fresh in incubation buffer at the time of each determination and protected from light. Reactions volumes were as follows: 200 μL of incubation buffer (50 mM Tris, 0.5 mM EDTA, 10 mM $MgCl_2$), pH 7.4 at 22 °C, 100 μL of test agent or serotonin (100 μM) or buffer (for total binding), 100 μL of [$^3$H]lysergic acid diethylamide (2 nM final concentration), and 100 μL of membrane preparation (15 μg of protein). The incubation was initiated by the addition of membrane homogenate and the plates were vortexed (Baxter S/P multitube mixer). The plates were incubated, with protection from light, by shaking (Gyrotop water bath/shaker model G76, speed 2) at 37 °C for 60 min. The binding reaction was stopped by filtration. The samples were filtered under vacuum over 96-well glass fiber filters (Packard Unifilter GF/B), presoaked in 0.3% PE1 in 50 mM Tris buffer (4 °C, pH 7.4) for at least 1 h, and then washed six times with 1 mL of cold 50 mM Trls buffer (pH 7.4) using the Packard Filtermate 196 harvester. The Unifilter plates were dried overnight in a 37 °C dry incubator. The Unifilter bottoms were sealed and 35 μL of Packard MicroScInt-0 was added. The plates were allowed to equilibrate for 1 h and were then sealed using a Packard TopSeal P with the Packard Plate Microvate 496. Plates were counted in a Packard TopCount 4.1 by liquid scintillation spectrometry. Each well was counted for 3 min. The test agents were initially assayed at 1000 and 100 nM. If the compound was activ (defined as causing at least 80% inhibition of [$^3$H]lysergic acid diethylamide binding at 1000 nM), it was further tested for determination of a $K_i$ value. The range of concentrations was chosen such that the middle concentration would produce approximately 50% Inhibition.

**Receptor Screen.** Assays for the following receptors were performed by the NIMH Psychoactive Drug Screening Program: (1) serotonin receptors: h5-HT$_{1A}$, h5-HT$_{1B}$, h5-HT$_{1D}$, h5-HT$_{1E}$, r5-HT$_{2A}$, r5-HT$_{2C}$, h5-HT$_6$, h5-HT$_7$; (2) dopamine receptors: hD$_1$, rD$_2$, rD$_3$, rD$_4$, hD$_5$; (3) muscarinic acetylcholine receptors: hm$_1$, hm$_2$, hm$_3$, hm$_4$, hm$_5$; (4) nicotinic acetylcholine receptors: α2/β2, α2/β4, α3/β2, α3/β4, α4/β2, α4/β2, α4/β4; (5) vasopressin receptors: hV1, hV2, hV3; (6) opiate receptors: hμ, hδ, hκ; (7) transporters: hSERT, hNET, rDAT; (8) rNMDA; (9) rPCP; and (10) rH1-histamine. Detailed on-line protocols for the binding assays are described at: http://meds20785.cwru.edu/myweb/protocol.htm. For screening purposes, the ability of 10 μM of each compound (dissolved in 10% DMSO) was incubated with the appropriate receptor preparation and percent inhibition determined for duplicate determinations each performed in duplicate. Where > 50% inhibition of specific binding was measured, $K_i$ determinations were then measured by competition binding assays in which concentrations from 1 to 100000 nM were incubated in duplicate. For each $K_i$ value the data represent the mean ± SD of computer-derived estimates for $N = 4$ separate determinations. h5-HT$_6$ receptor assays were performed exactly as previously described.[34]

**Adenylate Cyclase Assay.** h5-HT$_6$ receptors stably expressed in HEK-293 cells were grown in 24-well plates to near-confluency and 18 h prior to assay the medium was replaced with DMEM containing dialyzed 10% fetal calf serum. For the assay, the medium was aspirated and replaced with fresh DMEM without serum and incubated with various concentrations of test agent in a total volume of 0.5 mL for 15 min. The assay was terminated by aspiration and the addition of 10% trichloroacetic acid (TCA). The TCA extract was used for cAMP determinations. Data represent the mean of $N = 4$ separate determinations.

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